## REMARKS

### I. Status of the claims

With the entry of this amendment, claims 1, 4-13, 15-16, 18, 20-21, and 23-26 are pending in this application. Claims 2, 3, 14, 17, 19, and 22 are canceled without prejudice and disclaimer of the subject matter. Claims 18 and 20-21 have been withdrawn from further consideration as being drawn to non-elected subject matters, however, Applicants intend to rejoin the claims at appropriate time. Therefore, the withdrawn claims are being amended in parallel with the elected claims. Claims 24-28 are new.

Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, claims 1, 4, 7-13, 15-16, 18, 21 and 23 are amended to more particularly describe the subject matter of the invention. Applicants also add claims 24-28 to more particularly describe the subject matter of the invention. Support for these amendments can be found, for example, as follow:

| Claims | | Support |
|---|---|---|
| claim 1 | "immunoglobulin" | original claim 14 and specification at page 5, lines 14-15 |
| | "proline" | original claim 3 and specification at page 4, line 7 |
| | "wherein the preparation does not comprise nicotinamide" | specification at page 4, lines 9-10 |
| claim 4 (amended dependency) | | original claim 4 |
| claim 7 | | original claims 3 and 7 |

| Claims | | Support |
|---|---|---|
| claim 8 | | specification page 5, line 26 to page 6, line 8 and original claim 3 |
| claim 9 | | original claims 3 and 9 |
| claims 10-13, and 16 | | original claim 14 and specification at page 5, lines 14-15 |
| claim 15 (amended dependency) | | original claim 15 |
| claim 18 | "immunoglobulin" | original claim 14 and specification at page 5, lines 14-15 |
| | "proline" | original claim 3 and specification at page 4, line 7. |
| | "wherein the preparation does not comprise nicotinamide" | specification at page 4, lines 9-10 |
| claim 21 | | specification at page 7, lines 3-11 |
| claim 23 | | original claim 23 |
| claim 24 | "decreasing aggregate formation and/or of decreasing colouring of immunoglobulin preparations" | specification at page 4, lines 16-32 and at pages 11-12, Example 3 and Table 1 |
| | "comprising providing an aqueous immunoglobulin solution and adding one or more stabilisers chosen from non-polar amino acids" | specification at page 4, lines 2 to 3. |
| | "wherein the pH of the solution is adjusted to a pH of about 4.2 to 5.4" | specification at page 5, lines 28 |
| claim 25 | | specification at page 5, lines 31-32 |

| Claims | Support |
|---|---|
| claim 26 | specification at page 7, lines 9-11. |
| claim 27 | specification at page 6, lines 5-8 |
| claim 28 | specification at page 6, lines 7 |

Accordingly, no new matter has been added by the entry of these amendments.

## II. Specification

Applicants replaced the word "discoloring" with "coloring" on page 4, line 29 of the specification. Support for this amendment can be found, for instance, in the paragraph following the amended paragraph at page 5, lines 5-8: "[d]ecreased colouring preferably means that the optical density of the formulations of the invention is between about 20% and 60% lower than of conventional formulations." In addition, in the specification at page 11, lines 18 to 21: "[t]he glycine formulations exhibited optical densities that were between 25% and 48% higher than the corresponding proline formulations. These results provide further evidence that proline is a better stabiliser than glycine in IgG solutions." Such description explicitly support the notion that the present application is intended to decrease the coloring and not the discoloring of the immunoglobulin solution. Therefore, no new matter has been introduced by the entry of this amendment.

## III. Information Disclosure Statement

The Examiner acknowledges Applicants' Information Disclosure Statement filed on May 16, 2006 ("IDS") but requests Applicants to provide English translations of two

non-English foreign documents: EP 0 528 313 and EP 0 852 951. See Office Action, page 2. In response, Applicants submit that they have already provided copies of the English language counterparts of these two documents, namely, U.S. 6,303,113 and CA 2 272 245, respectively. Accordingly, Applicants have satisfied the Office's requirements with respect to non-English foreign documents. Consideration of those documents by the Examiner and appropriate notation of that consideration is respectfully requested.

## IV. Oath and Declaration

The Examiner indicates that "the oath filed on August 16, 2006 contains non-initialed/non-dated alterations." Office Action at 2. Solely to advance the prosecution of the present application, Applicants hereby submit a new oath in compliance with 37 CFR 1.67(a). Accordingly, Applicants request that this objection be withdrawn.

## V. Rejections under 35 U.S.C. § 102

### A. WO 98/28007

The Examiner rejects claims 1, 2, 5-8, 10, 12 and 23 under 35 U.S.C. § 102(b) as being anticipated by International Patent Application Publication No. 98/28007 to Dibiasi et al. ("the '007 publication"). Office Action at page 3. Applicant submits that the rejection is now moot in light of the presently pending claims for at least the following reasons.

In order to show anticipation, the Examiner must show that a single reference discloses, either expressly or inherently, each and every element of the pending claims. *See* M.P.E.P. § 2131. As acknowledged by the Examiner, the '007 publication teaches

an interferon-β formulation comprising glycine and/or arginine at pH 5.0 in a stabilizing buffer. Office Action at page 3. The '007 publication, however, is **not** directed to a immunoglobulin preparation as recited in the presently amended claims. In addition, nowhere in the '007 publication teaches that proline can be used as a stabilizer. Indeed, the '007 publication specifically teaches that "[t]he most preferred stabilizing agent for the present invention is an amino acid that may including one of the following: any **acidic** amino acid (e.g., glutamic acid, aspartic acid) or an amino acid selected from arginine and glycine." '007 publication, page 11, lines 5-8 (emphasis added). Proline, on the other hand, is not an acidic amino acid, but is instead a neutral, aromatic, hydrophobic amino acid. *See* The Molecular Biology of the Cell (2nd edition, Bruce Alberts et al. ed.), at 55 (1989), copy attached. Accordingly, the '007 publication does not teach each and every element of the present application, withdrawal of the 102 rejection is respectfully requested.

**B. U.S. Patent No. 5,831,736**

The Examiner rejects claims 1, 2, 5-8, 10, 12 and 23 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,871,736[1] to Bruegger et al. ("the '736 patent"). Office Action at page 3. Applicants respectfully submit that this rejection is obviated by the amendment adding "wherein the preparation does not comprise nicotinamide" to independent claim 1 and "the final concentration of proline is between

[1] In the Office Action, the Examiner has cited U.S. Patent No. 5,831,736, entitled "Method and apparatus for generating a three-dimensional topographical image of a microscopic specimen", in asserting both the 102 and 103 rejections. See Office Action, at pages 3-4. As this reference appears to be irrelevant to the present application, Applicants assume the Examiner has inadvertently cited the incorrect patent number and in fact intended to cite the IDS reference, U.S. Patent No. 5,871,736 to Bruegger et al., clarification of the records is respectfully requested.

0.2 to 0.4 M" to independent claim 8.

First, the '736 patent does not teach the exclusion of nicotinamide in a immunoglobulin preparation. On the contrary, the '736 patent teaches that:

> Preferred stabilizers are compositions **comprising nicotinamide together with one or more of the above amphiphilic amino acids or their derivatives.** More preferred stabilizer compositions comprise nicotinamide and proline, optionally together with one or more additional amphiphilic amino acids. Especially preferred compositions are mixtures of (a) nicotinamide and proline; (b) nicotinamide, proline and isoleucine; and (c) nicotinamide, proline, isoleucine and leucine. Preferably in such compositions the mole ratio of nicotinamide to total amphiphilic amino acids lies between 1:1 and 1:4. The most preferred composition is a mixture of nicotinamide, proline and isoleucine, preferably in a mole ratio of 1:(0.8-2.0):(0.8-2.0).

'736 patent, col. 4, lines 28-40 (emphasis added). In addition, as shown in the Table 2 and Table 5 of the '736 patent, in each and every instance, proline was used in conjunction with nicotinamide and not alone as a stabilizer. The '736 patent does not disclose a stabilizing composition that excludes nicotinamide and relies only upon proline. In view of the teachings set forth in the '736 patent, a skilled artisan would perceive that nicotinamide is required for stabilizing the immunoglobulin and would regard the exclusion of nicotinamide unfavorable for immunoglobulin preparations. For at least this reason, the '736 patent cannot anticipate the present application.

Moreover, the '736 patent does not teach the recited concentration of the proline in the amended independent claim 8. In fact, nowhere does the '736 patent teach or suggest that the final concentration of proline should be between 0.2 M to 0.4 M. Indeed, the '736 patent merely discloses proline concentrations of up to 0.2 M (See

Tables 2 and 5 of the '736 patent). For this additional reason, the '736 patent does not disclose every element of the present application, withdrawal of the 102 rejection is respectfully requested.

## VI. Rejections under 35 U.S.C. § 103

### A. WO 98/28007

The Examiner rejects claims 1 and 10-13 under 35 U.S.C. §103(a) as allegedly being unpatentable over the '007 publication. Office Action at page 4. Applicants submit that the rejection is now moot in light of the presently pending claims. As discussed above, '007 publication is not directed to an immunoglobulin preparation and does not teach the use of proline as a stabilizer. Furthermore, because interferon-β is different from immunoglobulin, both structurally and functionally, and different proteins often require different preparation strategies to attain optimum stability, a skilled person in the art would not anticipate a preparation method suitable for interferon-β be equally effective for immunoglobulin. Besides, the '007 publication merely discloses the benefit of using glycine and arginine (i.e. acidic amino acids) as a stabilizer and provides no motivation to a skilled artisan to use proline, a neutral amino acid, as presently claimed. There is no reason that the skilled artisan would apply the stabilization strategy for interferon-β to the antibodies of the present invention. Additionally, even if the skilled artisan did use the teachings of the '007 publication, the prior art teaches using very different amino acids and there would have been no reason to substitute proline for the acidic amino acids of the '007 publication. For at least these reasons, Applicants respectfully request the 103 (a) rejection be withdrawn.

**B. U.S. Patent No. 5,831,736**

The Examiner rejects claims 1, 5, 6, 10, 12, and 13 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '736 patent. Office Action at page 4. Applicants respectfully disagree and traverse the rejection for at least the following reasons.

In determining the differences between the prior art and the claims, "the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." M.P.E.P. § 2141.02(I) (Rev. 6, Sept. 2007) (emphasis in original) (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983). Furthermore, "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (emphasis added).

As discussed above, the '736 patent does not teach the exclusion of nicotinamide in a immunoglobulin preparation. In contrast, it specifically teaches a person to include nicotinamide in immunoglobulin preparations. *See* '736 patent, col. 4, lines 28-40. In view of the scope and content of the '736 patent as a whole, one skilled in the art, at the time the invention was made, would not have had any reason nor motivation to exclude nicotinamide for a immunoglobulin preparation as presently claimed. In fact, a skilled artisan would think that nicotinamide is necessary or beneficial for a immunoglobulin preparation and be discouraged from considering the removal of nicotinamide. The '736 patent teaches away from the presently claimed invention.

To demonstrate that the exclusion of nicotinamide and the use of proline alone in a immunoglobulin preparation leads to unexpected and better results, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 of the inventor, Dr. Reinhard Bolli ("Declaration"). As described in the Declaration, the stabilizer of the invention was compared to the prior art. Dr. Bolli and his laboratory formulated 10% IgG solutions with proline alone, nicotinamide alone, or combination of proline with nicotinamide, at concentrations of 0, 125, 250, 350, and 500 mmol/L and pH of 4.8 ± 0.2. See Declaration, paragraph 10. After incubating the IgG solutions for 30 days at 40°C in the dark, the aggregate formations and yellowish coloring of these different formulations were measured and compared. *Id.* As shown in Table 1 and Figures 1-2 of the Declaration, after 30 days of incubation, the immunoglobulin formulations with proline alone had lower amount of aggregates and less degree of coloring as compared to the formulations with nicotinamide alone or the formulations with both proline and nicotinamide. As stated by Dr. Bolli at paragraph 11 of the Declaration, such results are unexpected in view of the teachings of the '736 patent, which taught using proline and nicotinamide together for stabilizing immunoglobulin but did not teach or suggest that proline alone can be used for decreasing aggregate formation and for decreasing the coloring of the IgG solutions. As one of ordinary skill in the art would not have known that proline alone can be used as a stabilizer and would be surprised by the results that show exclusion of nicotinamide decreases aggregate formation and coloring of immunoglobulin solutions, the Declaration supports Applicants' position that the claimed invention would have not have been obvious.

In addition, the claimed invention is novel and unexpected in view of the concentration range suggested by the '736 patent, which merely discloses a proline concentration up to 0.2 M. As further described in the Declaration, Dr. Bolli and his laboratory measured and compared the dimer formations in 10% IgG solutions with 0, 125, 250, 350, and 500 mmol/L proline over time. *See id.* paragraph 12. The results shown in Figure 3 of the Declaration indicates that, in terms of dimer formation, immunoglobulin formulations containing proline at a concentration within 0.2 to 0.4 M work considerably better than the formulation having no proline or proline concentration at 0.125 M. However, having proline concentration at 0.5 M does not result in consistent and uniform decrease of dimer formation over time as shown in Figure 3 of the Declaration. Furthermore, as stated by Dr. Bolli, to the extent that the '736 patent merely discloses a proline concentration of up to 0.2 mM, a skilled artisan would have no reason nor motivation to increase the proline concentration beyond 0.2 mM because having higher proline concentration in the IgG solution would increase the cost of preparation and the osmolarity of the solution, both of which could lead to undesirable outcomes for clinical applications. *See id.* paragraph 13. Accordingly, the claimed invention is novel and unexpected in view of the concentration range suggested by the '736 patent. For this additional reason, a prima facie case of obviousness cannot be established in view of the '736 patent. Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

### C. '736 patent in view of '055 patent

The Examiner further rejects claims 1, 10, and 11 under 35 U.S.C. §103(a) as allegedly being unpatentable over the '736 patent in view of U.S. Patent No. 6,252,055 to Relton ("the '055 patent"). Office Action at page 5. Applicants respectfully disagree and traverse the rejection for at least the following reasons.

As discussed above, the '736 patent teaches neither the exclusion of nicotinamide in a immunoglobulin preparation nor the recited concentration of proline in the preparation. The '055 patent does not cure these deficiencies. Indeed, the Examiner merely relies on the '055 patent with respect to its alleged teaching of IgG concentration for subcutaneously administration. Accordingly, the combination of references does not render obvious the claimed invention. Applicants respectfully request that this rejection be withdrawn.

## VII. Conclusions

In view of the foregoing remarks, Applicants submit that the claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration of this application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

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By: Rebecca M. McNeill
Rebecca M. McNeill
Reg. No. 43,796